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UNIVERSITY OF TORONTO
MEDICAL JOURNAL

ESTABLISHED DECEMBER 1923
AN UNDERGRADUATE PUBLICATION

VOLUME XXXII NUMBER 5
TORONTO, MARCH 1955

ENDOCRINOLOGY

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This Journal is published six times a year from November to April, by the Medical Society of the University of Toronto, to serve primarily as a medium for student expression.
Subscription Rates: $3.50 for one volume of six consecutive issues. Single copies 65¢.

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EDITORIAL

When we consider the practice of medicine, three types of practice may be distinguished: common sense practice, empirical practice, and modern scientific practice. These are employed in varying degrees in all phases of medicine, but the past fifty years have brought about a considerable decline in empirical or trial and error practice and in common sense practice with its reliance upon the special experience of the individual doctor. On the other hand, there has been a concomitant advance in the calibre and extent of modern scientific practice; that is, in the application of theoretical generalizations to practical problems. In consequence, an astonishing rich and constantly increasing body of facts has been amassed; clinical analysis is more penetrating than it has ever been; instruments, techniques, and treatment have been immensely improved; and, as everyone knows, morbidity and mortality have been substantially diminished.

When compared to our own abundance, the past may seem very poor indeed. However, the significance of our wealth of facts must be interpreted with caution. It is generally accepted that the rise of science has been associated with a decline in moral purpose. This trend is of special significance in medicine. Examples of strength and nobility within the medical profession have not been due to technical skills alone, but to the combination of these skills with a higher degree of unselfishness and honesty than is common among men. Therefore, it follows that if the rise of this scientific approach has created moral problems, then the reflection of these problems in the field of medicine will be easily perceived. They are: the result is that articles critical of doctors are common in the popular press, and generally the inference might be that the public is presently unhappy with doctors. The interesting point is that people take all our hard-won technical advances for granted. They are disappointed and disgruntled to find that most doctors have human failings and that they share the modern desire to work fewer hours for greater reward. On the other hand, these same people are apparently content to believe that morals are founded on the shifting sands of human nature. But somehow the doctor is to be dedicated to a purpose and to practice a fixed and dependable morality. He must believe that the most satisfying existence is to forget his own happiness and work for that of others.

That this point of view is unfair to doctors is obvious. Nevertheless, it does emphasize that traditional medical practice has been a humanitarian art which adopted scientific procedures, and not a scientific art with a veneer of humanitarianism. It does not recognize the strange irony which is involved. The rise of science in medicine by opening the almost unlimited opportunity to expand the present range of medical treatment, offers, at the same time, the means to evade the effort of conscientious thought which the full and satisfying practice of the art demands.

It is true that the concentration of medical teaching upon facts and techniques and the specialization which this implies, is aptly defended on the ground that modern practice requires it. However, to build up technical competence without the corresponding development of moral purpose is not only at variance with the professed aims of medical education but is also unequivocally wrong.

All medical schools attempt to meet this problem by requiring varying amounts of liberal arts education. However, it would seem apparent that the sole restricted to the liberal arts college. It rests with the clinical teachers and, indeed, with the student himself.

R. E. W.

ACKNOWLEDGMENT

The Editor wishes to acknowledge the kind assistance and advice of Dr. E. R. Yendt, Resident Physician at the Toronto General Hospital, during the preparation of this issue of the Journal.

RECENT AWARDS

The following awards have been made:

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STAFF-STUDENT SMOKER

The Medical Society held its Annual Staff-Student Smoker on Thursday, Feb. 3, at Malloney's Art Gallery, with approximately thirty-five staff and two hundred students present.

Dr. J. Markowitz, Associate Professor of Physiology who was the guest speaker, delivered a most stimulating and enjoyable address. He spoke of his war-time experience as a prisoner-of-war in the Burmese jungle and how all possible medical and magical knowledge and common sense had to be utilized to survive. The speech was well documented with apt anecdotes and unexpurgated Aesop's Fables faithfully translated from the original tongues.

I. V. P.

THE EXPERIMENTAL AND CLINICAL ASPECTS OF GROWTH HORMONE

L. CHAIKOF, B.A. and R. SEAVER, B.A., 5T6

IN the last few years the effects of the growth hormone have been studied intensively in laboratories and in clinics. Much of the experimental work has been fruitful but the clinical results have been disappointing. It is one of the few hormones about which much is known experimentally, but for which no definite clinical application has as yet been found.

The early work of Evans and Long, and Smith showed very convincingly that the anterior pituitary secretes a hormone which possesses growth promoting activity. However, the question as to whether the anterior pituitary produced a specific growth hormone was a matter of controversy for many years. It was claimed that the inhibition of growth following hypophysectomy and the induction of overgrowth following administration of pituitary extracts resulted from a deficiency, or excess, respectively, of many or all pituitary factors, rather than a specific growth hormone. With the isolation from the beef pituitary gland of what appears to be a homogeneous protein, namely growth hormone, (Li, Evans and Simpson; Wilhelmi, Fishman and Russel; and Campbell and Davidson), which is capable of initiating and maintaining growth in hypophysectomized (hyped) rats, this evidence for a growth promoting hormone is now well supported.

The growth hormone is a protein elaborated by the eosinophil cells of the anterior pituitary gland. One of the methods by which the effect of this hormone can be demonstrated is by the over-all growth of the hyped rat as measured by weight and/or length. A more recent method is based on the action of growth hormone upon the epiphyseal cartilaginous discs of the long bones (tibia) of young hyped rats. In this "tibia test", the width of the uncalcified portion of the proximal epiphyseal cartilage of the tibia is measured and the increase in width is found to be proportional to the logarithm of the dose of growth hormone.

Growth and Protein Metabolism

Growth is a highly complicated phenomenon. It involves the laying down of new tissue. Measurement of body weight gain alone may be misleading, since the increase may be due to water retention, fat deposition, etc., as well as a true increment of the living tissue. Therefore, growth is associated with increased deposition of protein. This takes place with growth hormone in experimental animals. Young found that in both normal rats and dogs given growth hormone there was an increase in the total body water and tissue protein, but noted a loss of body fat.

Growth hormone has also a marked effect on skeletal growth, increasing the length of the bones in the limbs and axial skeleton. After hypophysectomy in rats, it is seen that a marked thinning of the epiphyseal cartilage plate occurs due to the decrease in number and size of the cells. The administration of growth hormone re-awakens chondrogenic and osteogenic processes to an extent comparable to that seen in normal growing rats, even after postoperative intervals of a year or longer. The plasma

alkaline phosphatase increases when growth hormone is given, indicating some relation of this enzyme to the process of bone transformation. However, not all growth phenomena are under the control of the pituitary. For example, the mitotic activity and regeneration of the liver following partial hepateetomy is only slightly impaired in the hyped as compared to the intact animal. Neoplastic growth is also to a large degree independent of the growth hormone.

After hypophysectomy, growth ceases in young rats, but the injection of growth hormone restores the growth rate even after the adrenal, thyroid and sex glands have totally atrophied. It has also been shown that growth hormone is effective in the absence of these target organs. However, this does not mean that the growth hormone activity is not influenced by the presence of other endocrine organs. The administration of thyroid hormone with the growth hormone causes greater increase in the dimension of the bones and in chondrogenesis and osteogenesis, than the administration of either hormone alone.

Recent work by Salter and Best has shown that the administration of insulin alone to hyped rats can induce growth as indicated by gain in body weight, nitrogen retention and increase in the cartilaginous plate of the tibia. Insulin can therefore act as a "growth" hormone in the absence of the growth hormone of the anterior pituitary gland.

The administration of growth hormone to intact animals increases nitrogen retention, which in turn increases the protein content of the body tissue. The coincident decreases in plasma amino nitrogen and non-protein nitrogen are probably related to the nitrogen retention and may be indicative of increased uptake of amino acids by the tissue eells. These changes may be interpreted as being eaused by either an increase in protein formation, by a decrease in protein destruction, or by both. The growth hormone decreases activity of arginase in the liver according to Frankel, Conrat, Simpson and Evans, indicating that the hormone has probably inhibited protein breakdown in this organ.

Milman, DeMoor and Lukens showed that in depancreatized animals on a constant insulin dosage, growth hormone caused a nitrogen retention which was only one-fourth of that caused by the same dose of the growth hormone in normal animals. They stated that this was strong indirect evidence that additional insulin is secreted by the pancreas in the normal animal in response to growth hormone. When the insulin was increased without giving growth hormone to the depancreatized animals, there was no change in the nitrogen balance. However, when the insulin was kept constant and the dosage of growth hormone given was varied, it was found that a large dose caused a greater retention of nitrogen than a small dose. This, therefore, suggests that growth hormone rather than insulin exerts the dominant influence on nitrogen storage, although ample insulin is necessary for an optimal response. It was also shown in depancreatized animals given growth hormone that by increasing the dosage of insulin up to three to five times the normal maintenance dose, normal nitrogen storage was obtained. They concluded that the normal animal secretes insulin in response to growth hormone and that the results with the increasing amounts of insulin used indicates the approximate magnitude of this increased secretion of insulin. In the same group of experiments, hyped-depancreatized cats (Houssay animals) were given large doses of growth hormone in the complete absence of insulin, and no nitrogen retention occurred. It might

therefore be assumed that the nitrogen-retaining and growth-promoting actions of growth hormone depend primarily on the availability of insulin secreted by the pancreas under the stimulus of the action of growth hormone.

Recent work by J. S. Munroe has shown that the continual loss of weight which occurred when dogs were placed on a low-calorie diet was prevented by growth hormone, but that no increase in weight occurred. Dogs put on a moderate diet and given growth hormone gained weight, while dogs given the hormone and a diet rich in calories and proteins gained weight twice as fast as those on a moderate diet. These animals which gained weight also showed a proportional increase in the amount of circulating protein and a corresponding rise in blood volume. Webb, Munroe and Campbell showed that the increase in circulating protein caused by growth hormone represented an increased synthesis of albumin and fibrinogen as well as a decrease in the rate of removal of globulin from the plasma. This might account for the increase in plasma volume due to increased osmotic pressure.

In other experiments, dogs fed on a rich diet began to show signs of diabetes on about the fourth day of growth hormone injections and the increases in body weight were reversed following the appearance of the diabetes. These series of experiments, therefore, demonstrate that the increase in body weight and plasma proteins is dependent on an adequate calorie and protein intake. When the diet is liberal in proteins, the protein synthesis is probably greatly increased. When diabetes ensues, the reduction in body weight is probably due to relative insufficiency of insulin. This is further evidence that growth hormone can only effect protein synthesis in the presence of an adequate supply of insulin.

F. G. Young has suggested that protein anabolism might even be more under the control of insulin and that the role of growth hormone on protein synthesis is of only minor significance. This is further borne out by the experiments of Salter and Best who demonstrated growth in hyped rats with insulin alone and by Young who showed that glucagon and insulin induced growth in hyped rats.

In addition to its effect on nitrogen metabolism, growth hormone influences the metabolism of phosphorus and sulphur. During growth hormone administration, the urinary excretion of inorganic phosphate, total sulphur and inorganic sulphate decreases and the plasma inorganic phosphorus level rises. These findings are similar to those which occur during protein synthesis.

Carbohydrate Metabolism

It has long been known that dogs treated with growth hormone develop glycosuria. Cotes, Reid and Young in 1949 succeeded in producing diabetes in cats treated with pure growth hormone and this has since been repeated by other workers. This raised the question of the relationship of the diabetogenic factor to the growth promoting factor. Reid showed that the diabetogenic activity of growth hormone paralleled its growth activity. Raben and Westermeyer claimed that they had separated the diabetogenic factor from the growth factor, and that their product was purely growth-promoting. This has not been confirmed by Reid and others. Ultracentrifuge and electrophoretic studies seem to point to a single factor. Although growth hormone is not diabetogenic in the intact rat, it will cause diabetes in partially-depancreatized rats.

The insulin content of the pancreas of dogs rendered diabetic by growth hormone falls, but in the intact rat, the insulin content almost doubles when growth hormone is injeeted.

In dogs given growth hormone, two phases of diabetes are produced, a reversible phase and an irreversible or permanent phasc. If the administration of growth hormone is diseontinued after *not more than one week* of treatment, the glycosuria disappears and the blood sugar returns to normal levels (reversible). If the growth hormone is given daily for prolonged periods, the diabetes may persist after discontinuing the treatment (irreversiblc). Histological examination of the pancreatie islets reveals degranulation and hydropic degeneration of the beta eells and eventually hyalinization and fibrosis. The diabctes produced by diabetogenic anterior pituitary extraets can be prevented by fasting, fat feeding and by the administration of insulin.

The mechanism by which growth hormone causes diabetes is not really understood but several theories have been proposed. One school maintains that growth hormone interferes with or bloeks the hexokinase reaction (glucose + ATP → glueose—6—phosphate + ADP) whieh is known to be stimulated by insulin; whether growth hormone is the agent responsible for this action is not yet established. If the reaction is bloeked, earbohydrate, instead of being utilised, is deposited in the tissues and aecumulates in the blood causing hyperglycemia and this, in turn, is the physiologie stimulus for islet eell secretion.

Recently, an anti-insulin hormone of the pancreas has been isolated ealled the hyperglycemic-glycogenolytic factor (HGF) or *glucagon*. It has been suggested that growth hormone stimulates the secretion of glueagon from the alpha cells of the islets of the pancreas and that glucagon, in turn, causes a hyperglyeemia and an increased demand for insulin.

That the diabetogenic action of growth hormone is not due to a direct stimulus on the islets has been indicated by the experimental work in which intravenous glucose was given continuously to induce a hyperglycemia. The resultant islet changes were the same as those seen when growth hormone was administered. The islet changes due to growth hormone can be reduced or prevented either by treatment with insulin or phloridzin. The latter, by lowering the kidney threshold, creates a glyeosuria without directly influencing intermediate carbohydrate metabolism.

Recent work by Chaikof and Campbell on growth hormone diabetic dogs (metahypophyseal diabetic dogs) has shown that when these dogs were receiving maintenanee doses of insulin, the injection of small doses of growth hormone for a period of four to five days caused an increased severity of the diabetes, but following this a permanent and signifieant decrease occurred in the insulin requirement of these dogs. These effects were also observed in depancreatized dogs, but the fall in insulin requirement was not so great as in the metahypophyseal diabetic dogs. Subsequent experiments eaused a further fall in insulin requirement(but not to as great an extent as the initial falls) until no further decrease in insulin requirement could be obtained. Biopsy of the pancreas of the metahypophyseal diabetic dogs did not show any evidence of beta cell regeneration. It was therefore suggested that the administered growth hormone caused a decrease in the output of growth hormone from the pituitary gland.

From all the above stated considerations, it might be concluded that the action of growth hormone in carbohydrate metabolism is of physiological significance, i.e. it has a hormonal role as an insulin antagonist.

Fat Metabolism

Fat metabolism is affected by growth hormone but the changes which occur are not well understood. It is possible that animals synthesizing protein at a greater rate than normal under the influence of growth hormone, and showing a diminished utilization of sugar, may be catabolizing their fat reserves at a minimal rate. It is known that marked lipemia may occur in normal and hyped animals treated with growth hormone.

Renal Function and Water Metabolism

The renal function of the hyped animal is markedly reduced, as evidenced by changes of glomerular filtration rate and renal plasma flow, and by derangements in its water metabolism (e.g., a decreased ability to excrete orally administered water). A growth hormone regimen elevates the renal function of hyped animals (dogs) to levels that are about 50% of normal. It also increases the ability of these animals to excrete an oral water load to about 75–80% of normal, and it raises the levels of the daily water exchange to those observed in experimentally induced diabetes insipidus. The urine excreted during such periods of polyuria has a very low specific gravity; it contains less nitrogen and urea than normal, no sugar, and less sodium than during the pre-growth hormone period.

Lactation

Recently another important function has been attributed to growth hormone, that of maintaining an adequate production of milk in lactating animals. This finding has caused revision of previous concepts about the initiation and maintenance of lactation, as both functions had previously been attributed to prolactin.

Clinical Aspects

The experimental results cited above indicate that the growth hormone might be of considerable value in the treatment of many clinical conditions. It might be expected to produce favourable responses in retarded growth or dwarfism and in syndromes characterized by a negative nitrogen balance. In view of its effects on carbohydrate and water metabolism, it should be of value in treatment of anterior pituitary insufficiency (Simmonds' disease). In therapeutic trials, however, *these expectations have not been realized.*

Bondy found that an injection of the hormone in volunteer subjects failed to produce changes in plasma amino acid, serum phosphate, insulin or glucose tolerances. If the hormone was injected rapidly, there was a ketosis. If injected slowly, the ketogenic action was less marked but a rise in blood glucose occurred. Since ketosis occurred before changes in carbohydrate and protein metabolism were evident, Bondy concludes that the basic effect of growth hormone is to promote fat utilization. Carbohydrate and protein are spared so that glycogen is stored and protoplasm is formed. Carballeira, Elrich and Browne administered infusions of amino acids intravenously, and after a single injection of growth hormone, observed an increased rate of removal of amino acid from the plasma and an over-all retention of amino acid nitrogen. The results are indicative of an increased rate of anabolism under the influence of growth hormone. Other workers have not been able to obtain positive results. If only a transient effect is produced,

the times at which samples are taken may be of utmost importance. This is particularly true when single injections are given, because the subject may have reverted to a normal state before determinations are made. In view of the diabetogenic effect of prolonged growth hormone administration, one would fear the production of diabetes mellitus in humans. As newer methods of separation and purification are devised, growth hormone may be produced with no diabetogenic activity. When such a preparation is available, investigators may be willing to initiate long term experiments on healthy subjects.

Many workers have tried prolonged administration in specific diseases such as hypopituitary infantalism, hyperinsulinism, anterior pituitary insufficiency, leukaemias and others. Many of these trials have been discouraging and the results have not been published.

Raben, Westermyer and Leaf tested a new preparation on a 26 year old girl with hypopituitarism. Intramuscular injection of 30 mg. per day caused retention of nitrogen and phosphorus. Daily injections as great as 240 mg. per day did not increase fasting blood sugar and glycosuria did not occur. The authors believe this work supports the view that the diabetogenic effect of pituitary extracts is separable from growth hormone. They appeared to be interested in testing the new compound rather than in treating the clinical condition. Escamilla and Bennett attempted treatment in a case of hypophyseal infantalism. The patient, when first seen, was a 16 year old girl, 49½″ tall. Previously she had been treated with many agents,—thyroid substance, pituitary tablets and injections, anterior pituitary extracts plus thyroid substance, and implants of fresh calves' pituitary gland. These were all ineffectual. Following 3 month control periods, she was placed successively on growth hormone, thyroid and methyltestosterone. Each caused only ⅜″ growth. She was then treated with thyroid and methyltestosterone which produced 1⅜″ growth in 3 months. This therapy was continued for 2 years during which time, the height increased by 6¾″ without advance in bone maturity. These authors suggest that growth hormone should have been employed in combination with thyroid.

Macdougall, Reid and Young report that in a patient with hyperinsulinism, whose symptons were not relieved by partial pancreatectomy, the administration of growth hormone caused transient hyperglycaemia. The patient was not cured, however and an islet cell adenoma was removed at a second operation. The authors considered that the cause of failure of the hormone to destroy the islet tissue was due to insufficient dosage, and suggested that growth hormone should have been combined with ACTH, since in experimental animals, the latter may potentiate the diabetogenic action of growth hormone.

It has been said that growth hormone does not exert much antigenic action, but some think that this may be a basis for treatment failure. It has been suggested that pyrexia, weight loss, nausea, vomiting, anorexia and lethargy in animals may be attributed to antigenic activity. These manifestations are not so severe with better purified (and consequently more potent) preparations. Some investigators feel that inadequate dosage differences between bovine and human growth hormone, impure preparations, and denaturation of protein may be factors in the ineffectiveness of therapeutic growth hormone in man.

Summary

This paper has attempted to elucidate
mone. A great deal has been published
the metabolic aspects of growth hor-

on the effects of growth hormone in animals, but very little is known about its effects on normal humans and in certain endocrine disturbances.

Acknowledgment

The authors wish to thank Dr. J. Campbell of the Department of Physiology, for his assistance in the preparation of this paper.

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THE CLINICAL ASPECTS OF ADRENOCORTICAL DISORDERS

B. LANGER, 5T6

THE modern era of clinical endocrinology was opened in 1855 when Thomas Addison published a paper on "Diseases of the Suprarenal Capsules" in which he described the disease which now bears his name. Since that time, a great deal of investigation has been directed toward the adrenal cortex and many clinical states, both real and hypothetical, have been attributed to its dysfunction. This paper will not attempt to discuss the recently propounded theory of Adaptation Syndromes, but will consider various clinical states known to be produced by specific adrenal pathology.

The chief manifestations of adrenocortical disease are due to either deficient or excess hormone production, thus they may be classified as diseases of hypofunction or hyperfunction.

*From an AOA symposium, Feb. 28, 1955.

Primary Adrenal Hypofunction

Primary hypofunction is due to a lesion within the adrenal itself, which causes decreased secretion of adrenocortical hormones in the presence of normal or even excess quantities of ACTH.

acute adrenal insufficiency

This occurs when the adrenals are largely destroyed by haemorrhage, infection, trauma, or surgical removal. The commonest example is the Waterhouse–Friedrichsen Syndrome, caused by a fulminating septicemia (usually meningococcal) and characterized by fever, cyanosis, petechiae, progressive circulatory collapse, and death, often within a few hours. Although in most cases there is massive haemorrhage into the adrenals demonstrable at autopsy, others which are identical clinically show little adrenal damage. This finding has cost some doubt on the importance of the adrenal in producing this syndrome. One explanation offered is that a *relative* adrenal insufficiency occurs in this type of overwhelming infection and may or may not be associated with adrenal destruction.

chronic adrenal insufficiency (addison's disease)

Etiology and Incidence The vast majority of cases are due either to bilateral adrenal tuberculosis or idiopathic atrophy. Other chronic destructive processes such as amyloid diseases and secondary carcinoma are rare causes. The peak age incidence is between 30 and 50; there is no sex preference.

Onset and Course The onset is usually a very gradual one and the patient may not seek medical aid until the full-blown picture has developed, which may be years after the first signs appeared. The course is a chronic downhill one, punctuated by acute exacerbations known as crises, during which the patient may succumb. Crises are precipitated by exposure to stresses such as infection, intoxication, overexertion, and especially surgical trauma. Occasionally, a crisis will be the first indication of the patient's disease.

Signs and Symptoms The features of the disease as first described by Addison are "anaemia, a general languor and debility, a remarkable feebleness of heart's action, irritability of the stomache and peculiar changes in the colour of the skin". With the exception of anaemia which is not a common finding, most Addisonians seen today present this same clinical picture.

There are two features which are almost constant findings in the disease, and without which the diagnosis must be questioned. These are pigmentation and arterial hypotension.

The *pigmentary changes* are believed to be related to a Melanocyte-Stimulating Hormone (MSH) secreted by the anterior pituitary and inhibited by the hormones of both the adrenal cortex and medulla. With adrenal destruction this inhibition is decreased and melanin formation is increased. The most significant change is the appearance of brown or blue-grey patches in the mouth. There may also be diffuse or patchy pigmentation elsewhere on the body, especially at skin creases, points of pressure, and in operative scars. Occasionally, areas of depigmentation may occur.

The *hypotension* of Addisonians is usually characterized by a postural as well as a static component. The blood pressure is commonly about 90/60 during the intercrisis phase, and falls to much lower levels during crisis.

The above combination of symptoms rarely occurs in other diseases and is fairly specific; the rest of the symptoms

are found in a variety of conditions and produce pictures which may especially be confused with advanced carcinoma, tuberculosis, and certain anxiety states.

Asthenia is present in all cases, is often the first symptom, and may become so severe as to be disabling. This weakness affects cardiac as well as skeletal muscle: the heart sounds are feeble and the pulse weak.

Gastrointestinal symptoms are first manfest as anorexia, and later progress to nausea and vomiting. There may be either diarrhoea or constipation, and occasionally there is severe abdonimal pain.

Weight loss is a characteristic finding and is a combination of tissue loss and dehydration. The tissue wasting results from the profound anorexia, while salt and water loss via the kidneys and through vomiting and diarrhoea accounts for the dehydration.

Mental irritability is a prominent symptom in some cases.

Crisis There are actually two forms of crisis; electrolyte and hypoglycaemic.

Electrolyte crisis is characterized by marked increase in severity of the gastro-intestinal symptoms, progressive dehydration and prostration. The blood pressure falls to very low levels: circulatory collapse and death may result.

Hypoglycemic crisis In three quarters of Addisonians there is a disturbance of carbohydrate metabolism, and about half of these have mild to severe bouts of hypoglycemia. In severe episodes there is progressive deterioration of consciousness which may go on to coma and death.

Laboratory Findings *Electroylte disturbances* occur in almost all cases. As a result of insufficient mineralocorticoids there is disturbed renal conrol of water and electrolytes, which causes depletion of serum sodium and chloride, elevation of serum potassium and haemoconcentration. During crisis the NPN may go up and occasionally there are manifestations of acidosis. Procedures such as the Robinson-Kepler-Power water test, or salt deprivation tests may also demonstrate impairment of water and electrolyte control.

The fasting *blood sugar* may or may not be low. Tests to demonstrate a hypoglycemic tendency include glucose tolerance tests, starvation tests, and insulin sensitivity tests.

X-ray of the abdomen may show calcification of the adrenals in those cases due to tuberculosis.

The *urinary output of adrenal steroids* over a 24-hour period is a direct indication of the secretory activity of the adrenal cortices, and is always decreased in Addison's disease. Also, there is no rise in the urinary steroids after administration of ACTH.

Secondary Hypofunction

Since the adrenals must be stimulated by ACTH to function normally, disease of the pituitary which causes decreased ACTH secretion will produce secondary adrenal insufficiency. In these cases, there is usually secondary hypogonadism and hypothyroidism as well. In some, there is specific evidence of a pituitary lesion. Urinary adrenal corticoid excretion is low but usually rises after ACTH administration. This test is used to differentiate primary from secondary adrenal insufficiency.

Adrenal Hyperfunction

In theory, there should be three primary diseases of hyperfunction, each caused by overproduction of one group of adrenal hormones; glucocorticoids, mineralocorticoids, or sex steroids. In practice, however, this is not the case and adrenal hyperfunction produces a

variety of clinical pictures, each depending on the combination of hormones produced in excess and also their relative quantities. Two fairly distinct clinical pictures, however, may be considered as representing opposite ends of this series:

1. Cushing's Syndrome, in which the manifestations are chiefly those of glucocorticoid overproduction, and less signicantly mineralocorticoid and sex hormone excess.

2. The Adrenogenital Syndrome, which represents primarily excess production of adrenal sex hormones.

CUSHING'S SYNDROME

Etiology and Incidence The commonest causes of Cushing's Syndrome are hyperplasia of the adrenal cortices or tumour (either adenoma or adenocarcinoma). Some cases were formerly believed to be due to a basophile adenoma of the anterior pituitary with excess ACTH production and secondary adrenal overactivity. Others have been ascribed to a variety of causes, including carcinoma of thymus, pancreas, and lung, and lesions in the hypothalamus. The disease is five times as common in females as in males, and may occur at any age, although it is most frequently seen in the third and fourth decades.

Onset and Course The onset of symptoms is usually gradual, but may be abrupt, and in women, it is frequently marked by the occurrence of amenorrhea. Sudden weight gain may also be an early sign. The course of the disease depends largely on the underlying cause. Patients with adrenal carcinoma may die of their tumour in a few years, whereas with a benign lesion, they may carry on for many years and finally succumb to intercurrent infection or hypertensive complications.

Signs and Symptoms Certain of the signs and symptoms may be conveniently classified according to the specific hormonal effects which they represent:

1. The *protein antianabolic* effect of excess glucocorticoids produces signs of protein depletion in various tissues.

The muscles become wasted and there is weakness and easy fatiguability. The wasting is most marked in the limbs and is, in part, responsible for the appearance of trunk obesity.

The bones are osteoporotic due to deficient protein matrix; this is most evident in the spine and ribs. These patients frequently have a dorsal kyphosis due to compression fractures of their weakened vertebral bodies.

The skin is thin and frail. Protein loss plus stretching due to fat deposition are believed to produce the typical purplish striations, most commonly seen on the lower abdomen, breasts, and thighs. There is often marked facial plethora, and sometimes acne.

The blood vessels are more fragile. This is manifest by easy bruisability and occasionally the occurrence of petechiae or ecchymoses.

2. The *disturbance of carbohydrate metabolism* (increased gluconeogenesis and decreased peripheral utilisation of glucose), also due to excess glucocorticoids, tends to increase blood sugar levels. Thus patients often have hyperglycemia and glycosuria, and sometimes frank diabetes. The carbohydrate disturbance in some is minimal and may not reveal itself even on a glucose tolerance test.

3. The *effects of adrenal sex steroids* depend on the amount of hormone secreted, and are apparent in most female patients. Amenorrhea, as mentioned, is often the first sign of the disease, and later hirsutism may become a prominent and disturbing feature.

There may be changes in sex interests, and rarely homosexuality. In males, there is often some decrease in libido and rarely signs of feminization.

The remaining features of the disease are not classified as above, since they cannot be directly attributed to known hormonal effects.

Hypertension occurs in most cases of Cushing's Syndrome and may produce the same vascular lesions and complications as essential hypertension. The salt-retaining effect of the mineralocorticoids is believed by some to cause the increased blood pressure, while others postulate various adrenal vasopressor and nephrotoxic substances.

Obesity is typically confined to the trunk, neck, and face, and is associated with the striae already described. The face is rounded ("moon-shaped"), and a pad of fat on the back may give the appearance of the so-called "buffalo" hump. The weight changes are variable: in some, there is no fat deposition and the patient may lose weight, while at the other extreme, gains of over one hundred pounds have been reported. In these latter instances, salt and water retention as well as fat deposition are involved.

Mental and emotional changes occur often and vary from mild disturbances to overt psychoses. The most common condition seen is severe depression.

Of the above features of Cushing's Syndrome, the most striking clinically are the gross changes in appearance, and there may be some tendency to overemphasize them. It must be remembered that the diagnosis cannot be made on physical appearance alone, since occasionally patients with minimal overt changes suffer from the severe metabolic disturbances of the disease, and conversely, healthy individuals may show certain of the "typical" physical changes.

Laboratory Findings Electrolyte changes (sodium retention, potassium depletion) due to excess mineralocorticoids, and hemopoietic changes (eosinopenia, lymphopenia, leukocytosis, erythremia) due to excess glucocorticoids are inconstant findings and are usually of little practical value in diagnosis.

Findings which would strengthen a diagnosis of Cushing's Syndrome are: hyperglycemia or a diabetic type of glucose tolerance curve; and X-rays showing osteoporosis.

The most reliable evidence is, of course, actual demonstration of increased output of adrenocortical hormones. The average 24–hour urinary corticoid excretion is almost invariably raised and the 17–ketosteroids are usually elevated. In some cases, further information may be obtained by following the urinary steroids after ACTH administration.

In differentiating between adrenal tumour and hyperplasia, the above tests may be of value. Special X-ray techniques will sometimes demonstrate the presence of an adrenal tumour.

THE ADRENOGENITAL SYNDROME

The picture produced in an adrenogenital syndrome depends on three factors; the sex of the patient, the type of hormone producing the changes, and the age of onset of the disease.

The congenital form occurs in both males and females, and is caused by bilateral hyperplasia of the adrenals, secreting excess androgenic hormones. The female infants are pseudohermaphrodites and show changes varying from partial to almost complete reproduction of the sexual organs of the opposite sex. Commonly, the child appears to be a male with undescended testes and a hypospadic penis. The male infants reveal precocious sexual development.

Occasionally, with the hypersecretion of androgens, there is decreased secretion of the other hormones, particularly the mineralocorticoids. As a result, these infants lose sodium, chloride, and water through their kidneys, and may become severely dehydrated. (cf. Addison's Disease).

The elevated urinary 17–ketosteroids in this condition differentiates it from other types of pseudohermaphroditism.

In preadolescent children, the adrenogenital syndrome occurs in both males and females, and is caused by either adrenal tumour or hyperplasia, with the picture of excess androgen secretion in most cases.

In males, there is precocious sexual and physical development producing the picture of the "infant Hercules". Skeletal growth is rapid but ceases early, the muscles are large and strong, there is hair growth on the pubis, axillae and face, and enlargement of the genitals, but no spermatogenesis.

In females, there are the same growth changes accompanied by masculinization. The physique, voice, and hair distribution become male-like, and there is hypertrophy of the external genitals, especially the clitoris.

These cases must be distinguished from androgen-secreting tumours of the gonads and constitutional premature puberty. In rare cases, the adrenals may secrete estrogens and produce premature puberty in the female and feminization in the male.

Postpubertal adrenogenital syndromes are most frequently due to adrenal tumour. The majority occur in females, are androgen-secreting and produce amenorrhea, hirsutism, and male-like changes in voice, physique, and sex characteristics. Rarely there occurs an estrogen-secreting adrenal tumour, in a male, the signs of which are gynecomastia, feminization of physique and body hair, and decrease in size of the external genitalia. Psychic changes usually accompany physical changes in both sexes.

Measurement of the urinary 17–ketosteroids is of diagnostic value in the adrenogenital syndrome at any age. Androgen-secreting tumours of both gonads and adrenals tend to produce very high 17–ketosteroid levels, which are not affected by cortisone administration. If there is no mass detectable by palpation or by special X-ray techniques, differentiation between these two may require laparotomy. Where the syndrome is due to hyperplasia of the adrenals or constitutional premature puberty, the 17–ketosteroids are usually moderately elevated, and tend to fall after cortisone administration.

* * *

In conclusion, it is worth repeating that *the diseases of hyperfunction* are *not sharply divided* into the two types described above, i.e. Cushing's Syndrome and the Adrenogenital Syndrome. The vast majority of cases are a mixture of the two, and the number of different clinical pictures is limited only by the number of combinations of the symptoms of both syndromes. To complete this heterogeneous picture, local pressure symptoms or symptoms of metastases are occasionally seen. It should be mentioned in passing that non-functioning adrenal tumours do occur; adenomas not infrequently, carcinomas rarely.

Acknowledgment

I would like to thank Dr. M. W. Johnston for his assistance in the preparation of this paper.

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THE TREATMENT OF ADRENOCORTICAL DISORDERS

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TODAY, the correct treatment of the diseases of the adrenal cortex can save life, restore health, and in some instances give normal life expectancy to its victims. This paper will include the principles and recent advances in the management of the disorders of adrenocortical hypofunction and hyperfunction.

Disorders of Hypofunction

Chronic adrenal insufficiency, or Addison's disease, was described in its classical form in 1855. However, it was not until 75 years later, in 1930, that a cortical extract was prepared that could maintain life in an adrenalectomized animal. Following this, there developed an appreciation of the effect of adrenal extract on sodium and chloride metabolism. It was soon realized that salt was an important adjunct to therapy and also that excess potassium was dangerous to the patient. Further studies of the cortical extract demonstrated a substance which would cause retention of salt and the excretion of excess potassium. It was at this point that desoxycorticosterone was isolated and practical hormone therapy became a reality for the first time.

*From an AOA symposium, Feb. 28, 1955.

Desoxycorticosterone itself did not correct the many manifestations of disturbed carbohydrate metabolism, restore the sense of well-being, or correct the characteristically slow EEG as seen in untreated chronic insufficiency. Cortisone has completed these requirements by correcting hypoglycaemia and related defects in the metabolism of carbohydrate, protein, and fat, as well as restoring the EEG to normal, and the sense of well-being. It is still hoped that further studies may lead to more physiologically complete replacement therapy, and perhaps to a means of more efficiently estimating the quantities of hormones needed for ideal maintenance therapy.

ACUTE INSUFFICIENCY

Adrenal insufficiency may present as an acute emergency with the patient comatose and close to death. The condition requires immediate and vigorous therapy. Constant attention is necessary with careful recording of pulse, temperature, blood pressure and respiration. Therapy is directed along three lines:

1. Combatting the adrenal cortical insufficiency.

2. Management of shock.
3. Treatment of any infeetion.

On admission, a blood sample is taken for determination of electrolytes, sugar, and NPN, as well as for crossing and typing. Of eourse, the attendant must not await laboratory data before instituting therapy. An intravenous infusion of 5% dextrose in saline is started. 100 mg. of aleoholie solution of hydrocortisone is added to eaeh 500 ec. of fluid and run in in about 4 to 8 hours. This substanee is now available commercially in ampoules of 100 mg. in 20 cc. 50% alcohol. Because intravenous hydrocortisone has both a gluco- and mineralo-corticoid effect, it has supplanted the use of intravenous aqueous adrenal cortical extract plus intramuscular DOCA in the treatment of crisis.

Shock is treated with blood transfusion and noradrenaline.

Because Addisonian crisis is frequently precipitated by infection, the symptoms of which may be marked at the time of admission, antibiotics should be administered routinely.

The patient's progress is followed clinically with haematocrit determinations, weight and blood pressure reeords, electrolyte levels, intake and output charts, and estimates of gastrointestinal function. Intravenous fluids with hydrocortisone are eontinued until the patient can resume oral intake, at which time oral hydrocortisone or intramuscular cortisone plus DOCA (25–50 mg. I.M. daily) is substituted.

As the acute episode subsides, maintainance therapy is instituted. (q.v.)

In cases of acute insuffieiency seeondary to meningococeaemia, Kinsell suggests the use of an I.V. infusion eontaining hydrocortisone, ACTH, KCl and glucose, given along with intensive antibiotie therapy, and tube feeding of a high protein diet. Oral cortisone and intramuscular ACTH replace intravenous drugs as soon as possible and the hormones are gradually diseontinued over the next 4–5 days. Cortisone is discontinued before ACTH.

CHRONIC ADRENOCORTICAL INSUFFICIENCY

Some patients with this disorder may remain in apparently normal health without treatment, but even the most minor stresses of life may foree these people to bed or precipitate crisis. Therefore, they require the proteetion of therapy. Additional salt may control symptoms, but it must not be considered to be adequate therapy. Once instituted, maintainanee hormonal therapy must be eontinued throughout life.

Body weight, haematocrit, blood pressure, and heart size should be determined and used as a guide to dosage. Daily intramuscular injections of DOCA in oil should be given to determine optimal dosage. The daily dose varies from 1–5 mg. per day. The dose should be altered until weight and blood pressure are stabilized at the desired level. At the same time, cortisone is given orally in doses of 12.5–25 mg. daily. Dietary salt intake is kept eonstant. The symptoms of overdosage (hypernatraemia, oedema, cardiac enlargement, and weakness due to hypokalaemia hypertension) must always be kept in mind and watched for.

Onee the daily DOCA requirements are established, a long-acting preparation is substituted. Oral DOCA is ineffeetive and daily intramuscular injections are undesirable. Sublingual preparations eonsisting of compressed tablets of DOCA in propylene glyeol have been tried, but they are unsatisfactory as large doses are required and the taste is very objectionable.

The usual long-acting preparation used today is the subcutaneous implantation of DOCA pellets. These

pellets come in two sizes, 125 and 75 mg. The larger size is equivalent to an intramuscular dose of 0.5 mg. per day, and the number of pellets implanted depends on the previously determined daily requirements. The pellet is usually active for 8 to 12 months. Its advantages are decreased requirements due to the efficiency of utilization from continued absorption and the avoidance of injections. They have, however, certain disadvantages. A minor surgical procedure is required, and infection at the site of implantation with extrusion of the pellet may occur. Signs of overdosage require further surgery. Also, absorption becomes irregular in the last eight weeks of action, and symptoms of insufficiency may reappear. For these reasons, Thorn has recently advocated the use of a microcrystalline suspension of the trimethylacetate ester of desoxycorticosterone. Injections are given every four weeks. Maintenance of the clinical state is constant, and there are the advantages of infrequent injections, flexibility of dosage, and avoidance of surgery. A 30 mg. dose releases 0.6–0.8 mg. daily.

An easier and more practical method of establishing maintenance therapy is now being used in Thorn's clinic. The patient is started on 12.5–25 mg. cortisone daily and then given a 25 mg. (1 cc.) injection of the trimethylacetate ester of DOCA. He is carefully watched for effect, particularly around the fifteenth day (time of peak action) and at the end of the month. The next dose is then adjusted if necessary. Almost all patients can be maintained on 1–2 cc. of this preparation per month.

The hormonal requirements of patients with this disease are so variable that only the broad general principles can be outlined. Some patients may be managed with 25–50 mg. of cortisone daily; others require cortisone plus added salt and still others require both cortisone and DOCA. Only careful observation of the patient and his response to therapy will indicate the correct course to the physician. Cortisone sometimes produces mental changes necessitates low doses at the onset, or the use of hydrocortisone as a substitute.

It is of interest to consider that, as Addison's disease is often caused by tuberculosis, management of such a patient with an active focus elsewhere may pose quite a problem, in view of the fact that the use of cortisone in the presence of tuberculosis is contraindicated. Thorn, however, believes that cortisone in the small doses needed is justified in these cases and that the overall status of the patient is improved.

The efficacy of hormonal replacement therapy has made possible the removal of the adrenal glands in patients suffering from severe hypertension and from extensive secondaries from carcinoma of the breast or prostate. In these patients hormonal therapy begins on the day prior to operation (q.v.) to avoid postoperative adrenal crisis. Maintenance therapy is as outlined above, except that in the hypertensive group, DOCA should not be used because of its hypertensive effect.

ADRENAL INSUFFICIENCY SECONDARY TO PITUITARY INSUFFICIENCY

Theoretically ACTH should be ideal, but in practice it has proven to be unsatisfactory. Daily injections are required and the development of ACTH resistance has been observed. The simplicity of administration and the effectiveness of cortisone makes it the treatment of choice. If necessary, DOCA may be added.

It is the physician's duty in all cases of adrenal insufficiency to educate the patients thoroughly regarding their disease. They must be taught that

trauma, illness and surgery increase the need for hormones and that they require careful medical supervision at such times. They must be taught to watch their weight carefully and report any changes promptly.

Disorders of Hyperfunction

The manifestations of adrenal cortical hyperfunction (as outlined in the preceding article) range all the way from the adrenogenital syndrome at the one extreme to Cushing's syndrome at the other with many intermediate clinical pictures. The management of these two extremes is quite different.

ADRENOGENITAL SYNDROME

In females, the adrenogenital syndrome is manifested as pseudo-hermaphroditism, pre-natal virilism and post-natal virilism; in males, it is manifested as macrogenitosomia. These conditions are usually due to adrenal hyperplasia, producing an increased secretion of androgens as measured by urinary 17-ketosteroids. The object of therapy in these cases is to correct sexual malformations, control any concommitant adrenal insufficiency and to maintain normal rate and duration of growth. In 1951, Wilkins reported the results of therapy of six females and two male children with cortisone. In all the children, cortisone rapidly produced a decrease in 17-ketosteroids excretion from averages of 28–53 mg./day to 4–8 mg./day. The rapidity of decrease depended on the dose of cortisone. His series has since been enlarged with similar results.

He believes that the cortisone inhibits ACTH production and that this, in turn, leads to a decrease in adrenal hormone production. Once the level of excess androgens has been lowered, their inhibitory effect on pituitary gonadotrophins is eliminated. Release of the gonadotrophins leads to normal stimulation of the gonads and normal sexual development.

Wilkins has concluded that to prevent virilization, it is best to suppress as completely as possible abnormal androgenic activity. It is still too soon to tell the ultimate effect of this therapy on the adrenal cortex, but Wilkins found that even after several months of therapy, infection (i.e. stress) caused an increase in urinary 17-ketosteroids. Several months later, ACTH administered to such a patient caused a much smaller increase in the steroid excretion.

Wilkins believes that therapy will probably be necessary for very long periods and therefore the smallest possible dose should be used to bring the 17-ketosteroids below 8 mg./day in older children and as low as feasible in infants. The lower doses will also prevent much of the masking of infections, a decided disadvantage of cortisone.

Therapy should be started with high initial doses to bring down the 17-ketosteroids within five to ten days. In infants, this will require 25–50 mg./day in older children 50–100 mg./day. Intramuscular administration is better than oral, as it is more predictable. After the desired drop, maintenance doses are determined. Usually over the age of eight years, an intramuscular dose of 100 mg. every four days, is effective. In infants, one-quarter this dose is given. In young infants, a high salt diet and DOCA must be given as well if there is evidence of associated lack of gluco- and mineralo-corticoids.

In the females studied, breasts developed and vaginal smears showed oestrinization. There was a decrease in hirsutism. In the males studied, those who were 6–8 years old, with an

osseous maturity of 13–14 years, had rapid growth of testes with active spermatogenesis. Boys with an osseous maturity of less than 11 years, had no growth or maturation of testes. Wilkins concluded that the testicular maturation was not a direct result of the cortisone administered, but due to the pituitary gonadotrophin released when the excess secretion of androgens is supressed. The ability of the pituitary to secrete gonadotrophin is attained when the level of maturity, *as measured by the bone age*, is approximately 11–13 years.

In younger children, it is advisable to follow rates of growth and osseous development as well as 17-keto-steroids as guides to therapy.

If the virilism is due to tumour, benign or malignant, cortisone will have no effect of 17-keto-steroid excretion. The therapy in such cases is surgical and will be discussed below.

CUSHING'S SYNDROME

An identical clinical picture can be produced by tumour or by hyperplasia, although the latter is more common. Atlhough surgery is the only accurate means of distinguishing the two lesions, certain tests (mentioned in preceding article) may be very suggestive. At operation, one can determine the nature of the lesion by the appearance of the first gland visualized. One may see a true neoplasm, atrophy of the gland (indicating a tumour in the other gland) or diffuse hyperplasia which is almost always bilateral. Tumours are removed. If diffuse hyperplasia is diagnosed, 85–90% of the first gland is removed and the other gland is removed *in toto*. This fairly radical procedure is justified by the poor response of this disorder to medical therapy or radiation and by the poor prognosis in the untreated patient.

The results of surgery may be summed up as follows: If the syndrome is due to a benign neoplasm, complete remission will occur unless irreversible vascular changes have occurred. In hyperplasia, no response to therapy will occur unless very radical excision (as described above) is undertaken. In one series of forty-eight patients treated at the Mayo Clinic between 1945 and 1952 in the manner outlined, six died and forty had remissions lasting from 3 months up to 7 years. (at which time the report was written.) Since the original cause of the hyperplasia, whatever it may be, continues to exist, more recurrences can be expected with the passage of time. To obviate these recurrences, it has recently been advocated that complete bilateral adrenalectomy be done for this disorder. Other arguments advanced in favour of this procedure are that it avoids the hazard of relying on an insufficient remnant of adrenal cortex, that there is proven adequacy of modern substitution therapy for adrenalectomized patients, and that from the standpoint of homostasis it is better to remove the entire gland than to leave a small part near the adrenal gland.

The threat of postoperative adrenal crisis is present in all these cases and represents a very considerable threat to the patient's life. It is only since the correct procedures in preparing and carrying the patient through the immediate postoperative period, has been understood, that radical surgery on the adrenals has become a reality.

No extra hormone is required preoperatively as these patients have more than enough of their own. On the day of operation, the patient should receive 200 mg. of alcoholic solution of hydrocortisone intravenously, the infusion being started at the beginning of the

operation. The dosage is then tapered off gradually and replaced by oral cortisone or hydrocortisone.

In the immediate postoperative period, excess movement of the patient must be avoided to decrease the danger of hypotensive reactions. Neosynephrine may be required to control the hypotension.

If the adrenalectomy is complete, cortisone is gradually tapered to a maintenance dose. DOCA should not be given until the dose of cortisone is less than 75 mg./day and then only if serum sodium levels indicate its need. If the adrenalectomy is subtotal, cortisone only is given for one week and then the function of the remaining adrenal tissue is determined by the response to ACTH. The cortisone dose is adjusted or discontinued as indicated by this assessment.

* * *

Much progress has been made in the last few years towards the understanding and control of diseases of the adrenal cortex. It is to be hoped that future studies will lead to an even better understanding of the etiology and, physiology and treatment of these disorders.

THYROID FUNCTION TESTS

J. M. VALE, M.D.*

IN most patients, the state of thyroid function can be determined by means of the clinical history and physical examination. There is, however, a small group of patients in whom the diagnosis is difficult because of minimal alterations in circulating thyroid hormone, lack of the usual response of some tissues to altered hormonal levels or diseases simulating thyroid dysfunction. For example, mild hyperthyroidism may exist for a long period before it becomes clinically apparent. In older people particularly, the cardiovascular system may respond to increased circulating thyroxine before the other tissues show the typical manifestations of hyperthyroidism. The clinical picture of anxiety states and conditions associated with increased metabolism may closely resemble those of hyperthyroidism. Tests of thyroid function are of value not only in the diagnosis of mild or atypical thyroid dysfunction, but also in the differentiation between diseases due to the thyroid and others causing a similar clinical picture.

The four tests of thyroid function most commonly employed will be described. Each measures a different aspect of thyroid function and, partly because of this, each has definite advantages and disadvantages.

SERUM CHOLESTEROL

The normal total serum cholesterol ranges from 150 to 250 milligrams per cent.

The serum cholesterol is an indirect measure of thyroid function. Although it is well known that alterations in thyroid activity may affect the serum cholesterol level, the reason for this has not been determined. The serum cholesterol is usually elevated in hypo-

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thyroidism and is less consistently lowered in hyperthyroidism.

It should be remembered that the serum cholesterol is altered by many diseases other than those affecting the thyroid gland. Because the test is included in the routine of most hospital laboratories, it will prove useful in diagnostic problems when more direct methods of measuring thyroid function are not available.

BASAL METABOLIC RATE

The normal basal metabolic rate ranges from plus fifteen per cent to minus fifteen per cent.

It is a measure of the oxygen consumption of the patient in the basal state and is thus an indirect measurement of thyroid function, in that it determines the response (as shown by oxygen consumption) of the tissues to thyroid hormone. The apparatus must be maintained in good working order and it is of the utmost importance that the patient be in the true basal state. The latter implies a 12 hour fast as well as complete physical, mental and emotional rest. Accordingly, explanation and reassurance before the test are always necessary and repetition of the test on two or more occasions is often necessary.

The basal metabolic rate is elevated when there is an increase in circulating thyroid hormone. This occurs in hyperthyroidism, during the ingestion of moderate to large amounts of thyroid (thyrotoxicosis factitia), and in some patients with acute thyroiditis. In the latter disease, the inflammatory process causes disruption of the follicles and release of stored hormone into the blood stream.

The basal metabolic rate may be increased in conditions not associated with the thyroid gland. The most common of these is failure to attain the basal state. In polycythemia and leukaemia there is an increase in oxygen consumption. Dyspnoea associated with pulmonary diseases and cardiac failure increases both the respiratory rate and oxygen consumption. The basal metabolic rate is elevated during fever, after the injection of epinephrine or in the presence of epinephrine-secreting tumours such as pheochromocytoma. The increase in metabolism found in some cases of hypertension and of diabetes insipidus has not been explained.

The basal metabolic rate is lowered in primary myxoedema due to disease of the thyroid gland or in secondary myxoedema due to anterior pituitary insufficiency. On the other hand, a low basal metabolic rate may be found in the presence of normal thyroid function as determined by more direct tests. The low metabolic rate found in patients with marked obesity, severe malnutrition or fluid accumulation (as in anasarca) is an example of this. In addition, some patients with schizophrenia have a low metabolic rate. The reason for this is not known, but is being investigated in order to elucidate its relationship to aetiology and treatment.

SERUM PROTEIN-BOUND IODINE

The normal serum protein-bound iodine ranges from 3.5 to 7.5 micrograms per cent.

It is a measure of the actual amount of circulating thyroid hormone and thus is a direct estimation of thyroid function. Because of technical difficulties, it will be a long time before it supercedes the basal metabolic rate as a standard test. In the performance of the test, serum proteins are precipitated, carrying thyroid hormone down with them. Unfortunately, circulating iodine from any source is also precipitated and

may cause a false high value. The proteins are ashed, then dissolved, and iodine is estimated in the resultant solution by a sensitive colour reaction.

Since the serum protein-bound iodine measures circulating thyroid hormone, it is increased in hyperthyroidism, thyrotoxicosis factitia and sometimes in acute thyroiditis. Circulating thyroid hormone is also increased during the administration of oestrogen and during pregnancy. Another cause of an elevated protein-bound iodine is contamination by non-hormonal iodine, which is also carried in the blood in association with serum proteins. This is an exceedingly common cause of error because the sources of iodine are so widespread. These sources include tincture of iodine ingested or applied to the skin or mucous membranes; iodine-containing ointments such as vioform, suntan lotion, iodine-containing medicines such as cough mixtures, kelp and some vitamin preparations, and iodine-containing dyes used for X-rays, including myelograms, pyelograms and cholecystograms. Iodized salt does not contain enough iodine to affect the result. Inorganic iodines are eliminated in a few days or weeks, more quickly if the patient is hyperthyroid and the iodine turnover rapid. On the other hand, organic iodides are very slowly excreted and may affect the result for months. It is always necessary to inquire about these varied sources of iodine before taking blood for the determination of the protein-bound iodine and before accepting a high result as indicative of hyperthyroidism.

Fortunately, when iodine in excess of physiological need has been administered, the thyroid is full of iodine and will not take up a tracer dose of radioactive iodine. Thus, a procedure is available to confirm or disprove the presence of hyperthyroidism in patients in whom there is a high protein-bound iodine and a history of exposure to iodine-containing substances. The combination of high protein-bound iodine and low radioactive iodine uptake is found after the administration of iodine-containing compounds and large amounts of desiccated thyroid and in acute thyroiditis. Only in hyperthyroidism are both radioactive iodine uptake and serum protein-bound iodine simultaneously elevated.

A low level of circulating thyroid hormone and consequently a low value of the serum protein-bound iodine are found in myxoedema. The value is usually very low in primary myxoedema and it may be higher, but still subnormal, in secondary myxoedema. It may be low in the recovery stage of acute thyroiditis. Since the iodine is bound to serum proteins, low serum proteins will result in a low serum protein-bound iodine in the presence of normal thyroid function. Because mercury interferes with the colour reaction in the test, blood should not be withdrawn for the determination of the serum protein-bound iodine for several days after the administration of a mercurial diuretic. When the thiouracil group of drugs is administered, the serum protein-bound iodine serves as a measure of the suppression of thyroid activity. It will be normal on adequate doses of the drug and low if too high a dose is given.

Of the four tests under discussion, the serum protein-bound iodine is the only direct measurement of thyroxine production. The level does not vary directly with the clinical severity of hyperthyroidism. With a protein-bound iodine of 10 micrograms per cent, one patient may be very toxic and another only mildly ill. Tissue response to an increase in circulating thyroid hormone appears to vary a great deal from person to person.

RADIOACTIVE IODINE UPTAKE

Normal values for the 24-hour thyroidal uptake of radioactive iodine range from 14 to 40 per cent.

The radioactive iodine uptake is an indirect measurement of thyroid function since it measures the ability of the thyroid to trap iodine and not the ability to make thyroid hormone. These two functions usually, but not always, parallel one another.

Expensive equipment, special laboratory facilities and trained personnel are necessary for the performance of this test so that it is only available in larger centres. It is easy to perform and, like the serum protein-bound iodine, is independent of the mental and emotional state of the patient.

Radioactive iodine, with a half-life of 8 days, is shipped from Chalk River to Canadian centres once a week. After suitable measurement and dilution in a "hot" laboratory, tracer solution is made up. It consists of a small amount of the original shipment diluted with normal saline and autoclaved in rubber-stoppered vials. When first made up, the solution contains 3 microcuries of radioactive iodine per cubic centimetre. The patient receives 5 c.c. of this tracer either intravenously or by mouth. 24 hours later, the amount of radioactivity in the thyroid and in a control bottle containing 5 c.c. of the same tracer solution is measured with a Geiger or scintillation counter. The amount of radioactivity in the thyroid is expressed as a percentage of the administered radioactivity and this figure is the radioactive iodine uptake.

The amount of radioactive material employed in tracer studies, a maximum of 15 microcuries, does not result in any demonstrable radiation effect on the tissues. The excessive iodine not taken up by the thyroid is quickly eliminated in the urine. In some centres, the amount of radioactive material in the urine is measured rather than the amount remaining in the thyroid. A small dose of radioactive iodine ranging from 10 to 100 microcuries is always employed for tracer studies. On the other hand, therapeutic doses of radioactive iodine range from 3 millicuries upwards.

The radioactive iodine uptake is increased in hyperthyroidism and, as with the protein-bound iodine, the increase does not necessarily parallel the clinical severity of the disease. A high uptake is also found in areas of severe iodine deficiency. Under these circumstances, the high uptake of the iodine-starved gland is not a reflection of increased hormone production and it returns to normal when the iodine deficiency has been corrected. The thyroid glands of goitrous cretins also have an increased avidity for iodine, but probably lack some enzyme essential for its conversion into thyroxine. Rarely, in chronic thyroiditis the same dissociation of function is found.

In myxoedema, the radioactive iodine uptake is decreased. The very low values, 1 to 5 per cent, are usually associated with primary myxoedema and slightly higher but still subnormal values with secondary myxoedema. In primary myxoedema, the damaged thyroid is unable to respond to the administration of thyroid stimulating hormone. In secondary myxoedema, on the other hand, the "resting" thyroid responds with an increase in both radioactive iodine uptake and serum protein-bound iodine.

In acute and subacute thyroiditis, the injured gland initially releases stored hormone into the circulation, but is unable to trap iodine. With recovery, both the iodine-trapping and hormone-forming functions gradually return to normal, although there may be a temporary lag in the latter.

When large quantities of iodine are

administered the radioactive iodine uptake is decreased. It is also decreased during therapy with the thiouracil and sulphonamide drug groups. If the tracer is given during a period of diuresis, it may be washed out in the urine before the thyroid can take it up. Similarly, a tracer dose may diffuse into serous cavities if the patient is accumulating ascites or a pleural effusion. When desiccated thyroid in amounts equal to or exceeding the patient's endogenous production is administered, thyroid activity is suppressed and the uptake will be low. The gland may take weeks to recover normal function after cessation of thyroid therapy.

Tracer doses of radioactive iodine are also of value in detecting aberrant thyroid tissue in the neck and superior mediastinum. The rare functioning metastases of thyroid carcinoma may be located by scanning the body with a Geiger counter after a tracer dose has been administered. However, in most cases of thyroid carcinoma, the neoplastic tissue is unable to pick up iodine.

* * *

In summary, thyroid function tests are usually of great value. However, it should be remembered that each test has many pitfalls. Accordingly it is imperative that a careful clinical assessment be made of each patient.

STRESS ADAPTATION SYNDROMES

B. A. TOBE, B.A., 5T5

DURING the past fifteen years interest in stress and the adaptive hormones has grown markedly, due principally to the controversial work and writings of Dr. Hans Selye of the University of Montreal. He has been subjucted to severe and constant criticism, some of which is deserved and a great deal unwarranted.

Both in his thinking and in his work, Selye acts not as a clinician, but rather as an experimentalist. He obtains most of his data through the observation of experimental animals and tries to relate it to comparable conditions in humans. This forms the basis for much of the deserved criticism. It has been shown that each species of animal reacts in its own specific manner to stimulus. One cannot always predict the responses of a human being from the observed response of a guinea pig. Selye often deliberately ignores this important detail in trying to explain his theory and its many ramifications.

Thus when reading any articles, either by Selye or about his work, one must accept all theories and claims with reservation. Many of his early postulates have been shown to be without foundation and, in all probability, more will be proven erroneous. However, he still leads the way in providing a new and different basis on which to conduct research into endocrine balances and functions, particularly in relation to stress.

This paper is an attempt to serve as an introduction to the problems involved in stress, and to act as a basis for further readings in this field. It is designed neither as a criticism nor as a defence.

The term stress has been poorly defined. In its simplest sense it may be said to be a non-specific response to a

great many stressor agents (e.g., a bar of steel can be put under stress by both pressure and tension). The significance of the stress concept in modern medicine has yet to be realized; it may indeed be of prime necessity in understanding not only disease processes but, as Selye maintains, even life itself.

History

About 1880, Pasteur and his contemporaries introduced the concept of specificity into medicine; a concept which has proved itself to be invaluable to our present understanding of disease processes. He showed that an organism can develop specific adaptive reactions against individual pathogens, and that by imitating and complementing these reactions when necessary, we can treat many diseases which are due to these pathogens.

Selye proposes a negative counterpart or mirror-image to this long accepted concept. In formulating the adaptation syndrome, he suggests that many diseases have no single cause or specific pathogen, but are due to a non-specific stress and to pathogenic processes resulting from inappropriate responses to this non-specific stress. Of course, this idea did not originate with Selye. Pasteur himself realized and discussed the importance of the *terrain* in the development of specific diseases. Claude Bernard, the great French physiologist showed, in 1867, that to maintain life, the constancy of the *milieu interior* must be preserved despite a changing environment. This was followed by experimental work in many countries on seemingly unrelated observations. In the United States, Cannon, in 1922, described certain influences of adrenalin and the autonomic nervous system in maintaining this constant state; and Hartman, in 1932, discussed the role of *cortin* as a general tissue hormone necessary for the function of all cells. In 1934, Rene Leriche, a French surgeon, described his *maladie postoperatoire*, a clinical syndrome accompanying all types of severe surgical interference.

In 1936, it was demonstrated that an organism will respond in a stereotyped manner to a variey of widely different stressful agents as; infection, intoxications, trauma, nervous strain, heat and cold, muscular fatigue and radiation. Selye, among others, started to investigate the effects of adrenalectomy and hypophysectomy on these stereotyped responses, and found that the adrenal cortex was essential for them.

At the same time, due to the work of many investigators, particularly Reichstein and Kendall, pure cortical steroids and other hormones became available for use in both research and clinical studies. Because of this, experimental replicas of many poorly understood specific diseases could be produced by the administration of certain hormones. As the actions of ACTH, STH (somatotrophic hormone) the mineralocorticoids and the gluco-corticoids were observed and studied, the concept of the general and then of the local adaptation syndromes were formulated.

The Concept of the Adaptation Syndromes

That there can be both local and systemic non-specific reactions has been known for many years. However, it is only recently that the close relationship between the two has been established more clearly. According to Selye, the characteristic response of the body to systemic stress is the General Adaptation Syndrome (G.-A.-S.), while topical or local stress elicits a Local Adaptation Syndrome (L.-A.-S.) which is confined principally to the immediate vicinity of the eliciting injury.

Chronologically, both syndromes may comprise three distinct stages:

1. the alarm reaction (A-R), in which the adaptation has not yet been acquired
2. the stage of resistance (S-R), in which the adaptation is optimal
3. the stage of exhaustion (S-E), in which the acquired adaptation is lost.

The *alarm reaction* (A-R) can itself be divided into two phases: shoek and countershoek. The shock phase is the aeute initial period of the A-R, and is charaeterized by degeneration, necrosis and atrophy at both systemic and local levels. Here we may find either the typical clinical picture of secondary shock with a sudden severe systemic stress, or minimal tissue destruction and oedema with mild local injury as a splinter of wood. There is a stimulation of the autonomic nervous system and an outpouring of adrenaline together with other pathological changes; e.g. gastro-intestinal erosions, leucocytosis with eosinopenia, etc.

The phase of countershock is a defensive phase eharaeterized by an enlargement and increased activity of the adrenal cortex with an outpouring of many cortical hormones, a reversal of the acute changes seen during the shock phase, and involution of the thymico-lymphatic apparatus. This phase imperceptibly merges into the *stage of resistance* if exposure to the state of stress becomes chronie.

The *stage of resistance* (S-R) is characterized by an increased resistance to one particular stressor agent and a decreased resistance to all other stimuli. Thus adaptation to one agent is acquired at the expense of resistance to others. This resistance to other stimuli Selye terms *crossed resistance*. The typical pathological changes seen are those of hypertrophy and hyperplasia of

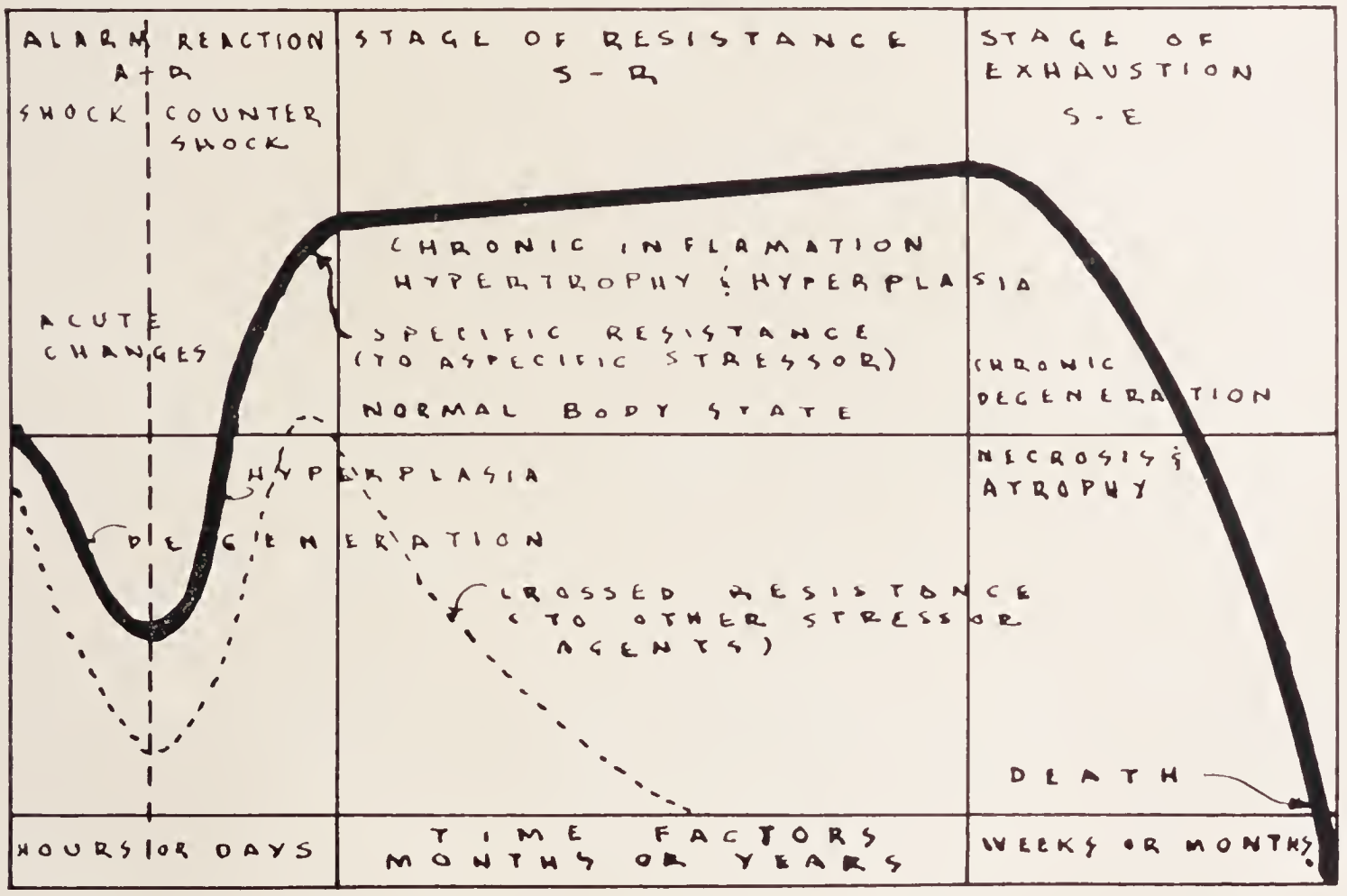

FIG. 1.—Illustrating the characteristic body responses occurring in the Adaptation Syndrome (adapted from Selye).

the organ-systems both at morphological and physiological levels.

The *stage of exhaustion* (S-E) develops ultimately as a result of prolonged over-exposure to the same stimuli or stressor agents. In this stage, the S-R adaptation can no longer be maintained. Even a perfectly adapted organism cannot indefinitely maintain itself in the stage of resistance; eventually the hypertrophy and hyperplasia of S-R will regress and the lesions characteristic of the A-R (degeneration, necrosis, atrophy) will reappear, leading to exhaustion and further resistance becomes impossible. Death must then shortly ensue if the stress remains.

The Mechanism of Adaptation

Before examining the roles the specific hormones may play in responding to stress, the general principles of stress-response must be understood. All agents which act upon the whole body or any of its parts exert both specific and non-specific effects. The specific actions are unimportant in this study except that they may modify the non-specific actions of these agents; e.g., ether causes anesthesia and may itself affect certain nervous and hormonal reactions.

The non-specific reactions are constant and of great importance. Unfortunately, not a great deal is known about the mechanisms of these responses. The stressor agent (e.g. a thermal burn) affects the target both directly and indirectly. The indirect responses can be mediated through nervous and humoral pathways. While a great deal of interest was centered on the neurogenic influences, it has now been shown that the G.-A.-S. can develop in the absence of all local nerve receptors.

The principal humoral pathways probably lead through the anterior pituitary gland and the adrenal cortex. The humoral transmittor substance responsible has been called the first mediator of hormonal defence, the nature of which is obscure. Indeed, there may be merely a constant effect elicited by many substances. The G.-.A.-S. can be produced by many compounds such as non-specific products of tissue catabolism, polypeptides, histamine and histamine-like compounds, adrenergic or cholinergic excesses and even sudden severe deficiencies of certain essential body constituents (glucose, enzymes, etc.). Selye, by using a "granuloma pouch," has shown that there is also an endogenous stimulant of inflammation in the development of the L.-A.-S. The same mechanism of mediation may be responsible for the development of both the local and the systemic stress responses.

The effects of the stress and the stereotyped reactions elicited are modified by many factors. The many specific effects of the causative agents must be integrated into this concept. They can be considered under three headings:

1. time—the duration and repetive nature of the stress
2. space—the location of the target or targets
3. intensity—the degree of activity.

Then there are the many conditioning factors of the host, some of which are external (diet—particularly salt and protein); temperature and light) while others are internal (heredity, constitution and previous exposure).

When a condition of stress exists, the anterior pituitary is probably stimulated by the first mediator to secrete more ACTH and possibly excessive amounts of STH. It is universally recognized that ACTH plays a major part in the regulation of the adrenal cortex, where two essentially antagonistic groups of corticoids are discharged. One group, the *mineralo-corticoids*, is currently attracting a great deal of interest and in-

vestigation. The only known naturally occurring member of this group is the recently discovered *aldosterone*. Desoxycorticosterone was also included until it was shown to be only a product of hormone metabolism. By the excessive administration of desoxycorticosterone acetate along with the surgical removal of certain tissues, Selye was able to produce experimental replicas of the so-called hypertensive and inflammatory diseases including nephrosclerosis, hypertension, periarteritis nodosa, and other rheumatoid and arthritic conditions.

The mineralo-corticoids may stimulate and enhance the proliferative ability and reactivity of connective tissue which is essentially a protective mechanism, and so have been termed *pro-inflammatory corticoids* (P-Cs).

The other group, the *gluco-corticoids*, (cortisone, hydrocortisone) tend to inhibit the growth of fibrous tissue, and may even cause involution of the previous connective tissue proliferation. They are essentially *anti-inflammatory corticoids* (A-Cs). Thus, while the P-Cs enhance the inflammatory potential of the body, the A-Cs depress it.

The effects of STH are not well understood. It is only recently that the purified hormone has become available for both experimental and clinical use, and that the name has been changed (by some investigators) from the growth hormone to the somatotrophic hormone.

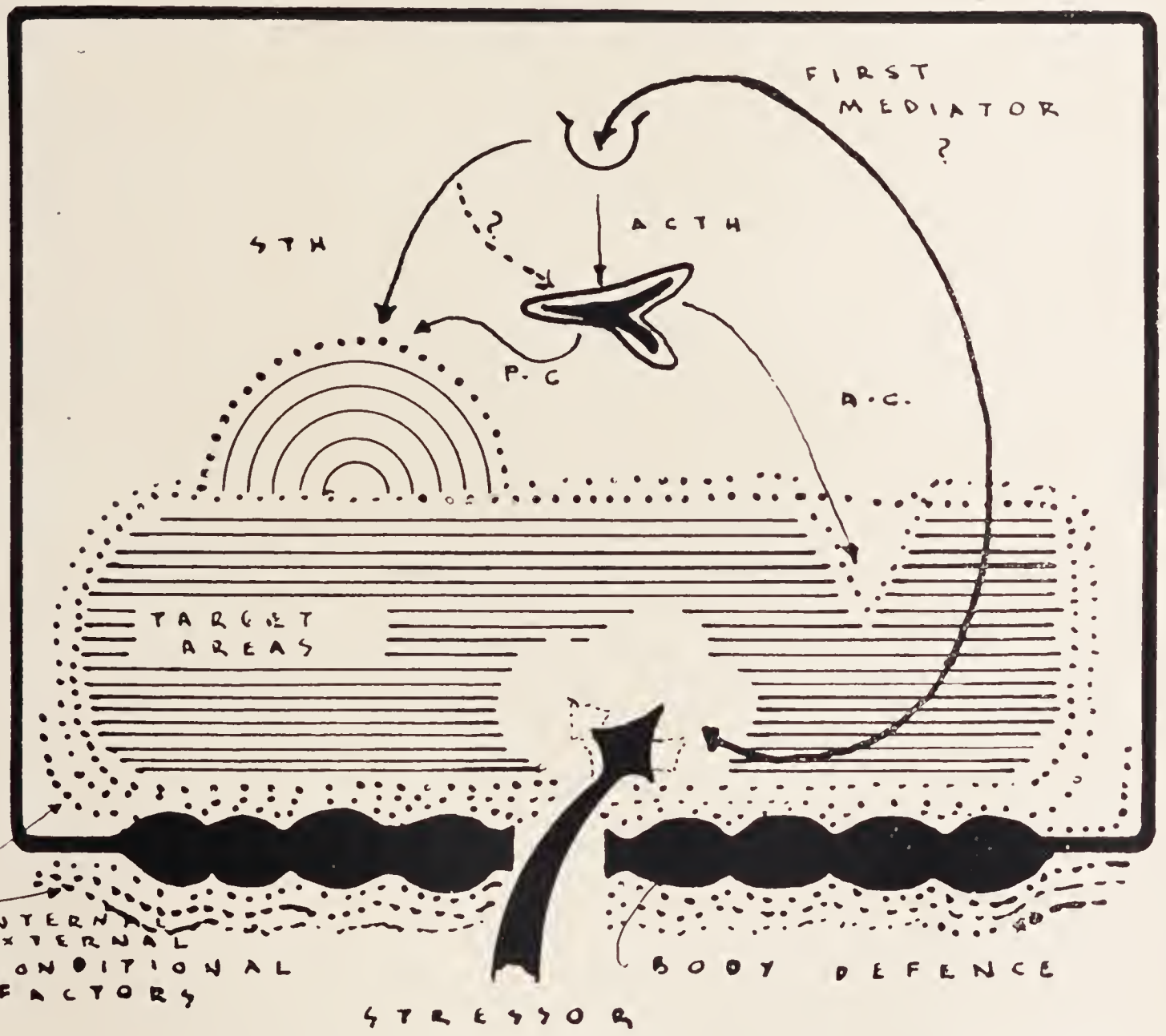

FIG. 2.—Illustrating the principal pathways of the stress response (adapted from Selye).

It may have an effect similar to the P-Cs in increasing the "inflammatory potential" of connective tissue. Two mechanisms for this action have been postulated. It may stimulate the adrenal cortex to produce selectively P-Cs, or more probably, act directly on the peripheral tissues by sensitizing them to the P-Cs. This suggests that STH could have no regulatory activity in itself, but be merely an important catalytic factor, by maintaining the target organs in a condition responsive to the P-Cs.

STH has been shown to have a very interesting and important role in the adaptation syndrome in that it effectively combats catabolism and the susceptibility to infections. ACTH on the other hand causes the body to lose weight and markedly increases the susceptibility to the usually non-pathogenic micro-organisms. The extent to which these actions of STH will prove of value in the management and treatment of acute fulminating infections and other conditions remains to be determined.

The exact mechanism of the adaptation syndrome depends upon the interplay between the many factors involved; the stressor agent(space, time and intensity), the conditioning factors (internal and external) and the hormones concerned. A state of stress can be produced in the body through multiple pathways, the effects being modified by the conditioning factors which vary in every individual, and in every part of the individual. These factors can affect both target and pathway selectively, and thus the manifestations of a single stress-response may be varied.

On the Nature of Disease

Efforts to arrive at a unified concept of disease have been made by physicians since the beginning of medical history. It has been suggested that the theory of the adaptation syndrome is an adequate basis for this unified concept. Indeed, the stress-response, with its systemic (G.-A.-S.) and regional (L-A-S.) manifestations, may encompass the very essence of what we call disease.

Disease can be considered to have a tripartite pathogenesis:

1. the direct action of the exogenous agent
2. the endogenous factors inhibiting this action
3. the endogenous factors facilitating this action.

On analysing these three components, we may diagnose a condition as inflammation and so treat it with either an anti-inflammatory hormone if the inflammatory process is undesirable, or a pro-inflammatory hormone if we feel that the process is essential.

Thus, it may be possible to develop a pattern of stress therapy. This therapy would not be specifically directed against any one pathogen, as are the chemotherapeutic agents, nor would it be symptomatic, eliminating only certain symptoms. The stress therapy would have to be *tactically defensive*, aiding the organism to adjust itself to both the systemic and local effects of the pathogen.

Certain pathogenic agents, called *unconditional pathogens* cause disease regardless of any conditioning or sensitizing circumstances. Examples of this are X-rays, mechanical injuries, and certain micro-organisms. However, most disease-producing agents are *conditionally acting pathogens* in that they are pathogenic only under special circumstances of sensitization. Here, both the pathogenic agent and the conditioning factors must all be present, since the full pathogenic situation must be realized before the disease can become manifest.

The cells as the morphologieal units of life do not all respond alike when subjected to similar stimuli. Even a single eell can respond with many quantitatively different biologic reaction-forms while undergoing adaptation to stress. If there is a universal basic adaptative reaction pattern, the eell cannot be the fundamental unit of living matter. There must be a subcellular unit whieh can still exhibit the generally aceepted characteristics of life. Selye terms this unit a *reacton.*

It is with the use of the reaeton as a eommon denominator that the concept of the adaptation syndrome may lead to a basis of a unified conecpt of disease. Then the surmise that all living processes are dependent upon merely quantitative variations in the activity of pre-existent elementary targets will be verified.

Acknowledgment

The author is indebted to Dr. J. C. Laidlaw who very willingly gave of his time and experienee to offer many invaluable criticisms and suggestions.

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THE ELLIOT P. JOSLIN CAMP FOR DIABETIC BOYS

E. J. G. NOBLE, 5T5

THE important role played by summer eamps in the physical and mental development of children has been well reeognized by both the general public and the medical profession. However, it has only been within the last few years that adequate summer camping has been made available to those children who, for financial or health reasons are unable to enjoy the great benefits of outdoor life. Last summer, it was the author's privilege to serve on the staff of such a camp; the Elliot P. Joslin Camp for Diabetic Boys. These are a few impressions of this rather unique institution.

The principles upon which the eamp functions are as follows:

First to enable diabetie boys from 5 to 16 years of age to enjoy the opportunities of wholesome camping, and at the same time receive complete medical and diabetie care.

Second to further the child's understanding of his condition in relationship to himself as well as to those around him.

Third to provide both theoretical and practical instruction in all phases of diabetie management in order that he may cope with his disease himself.

Fourth to keep an accurate, statistical record of all data pertaining to eaeh diabetic such as family history, onset of disease, insulin requirements, diet, exercise, complications, ete.; the critical analysis of such records in order to contribute to present-day knowledge of diabetes.

There is *one* requirement for enroll-

ment at the camp; the boy must have diabetes. The camp is non-sectarian and serves boys of all religious faiths from across the United States, Canada and the South Americas. Children also afflicted with other conditions, such as epilepsy, are not necessarily excluded.

In its seventh year of operation, the camp is a joint project of the Diabetic, Camp, Home and Hospital Fund (of which Dr. Elliott P. Joslin is Chairman of the Advisory Committee) and The Association of Universalist Women. Medical supervision is under Dr. Alexander Marble of the Joslin Clinic in Boston. The camp is run as a non-profit organization with fees payable by campers depending on their ability to pay. The 1953 operating cost per camper (including insulin) was approximately $55.00 a week.

LOCATION, FACILITIES AND STAFF

The camp is located high in the hills of Charlton, Mass., approximately fifty miles from Boston. There are approximately 115 acres of rolling country, including a small lake for water sports. The general plan of buildings is similar to that of most Canadian summer camps with the sleeping cabins accommodating eight campers and two counsellors each. In addition, there is a large infirmary and laboratory. Excellent facilities are available to the campers including land sports, handicrafts, dramatics and canoe tripping. One is amazed at the wide range of athletic facilities in a camp for supposedly sick children. Personnel include a director, business manager, 16 counsellors, 2 cooks, 3 laboratory technicians (mostly final year medical students), one resident physician and 3 graduate nurses.

GENERAL MANAGEMENT OF PATIENTS

The summer season is divided up into three sessions each consisting of three week periods with an average of about seventy campers at any one time; many of these remain for a second period. It is requested that parents accompany their children to camp so that a complete history and physical examination may be conducted in their presence, with specific attention being paid to previous diet, insulin intake, amount of exercise, degree of control etc. Then a complete urinalysis and haemoglobin determination are done. The subsequent camp routine is made to conform as nearly as possible to that of the average boys' camp, and the great challenge of allowing diabetic children a full range of activity, and at the same time maintaining adequate control of their disease was well met. From 7 a.m. to 9 p.m. each day, three periods of active exercise were so arranged as to decrease both insulin requirements and glycosuria. The average daily routine was as follows: after breakfast, one hour of vigorous exercise, such as basketball, baseball, etc.; then, until lunch, a less active period of shopwork, dramatics, etc. This sequence was repeated after lunch as well as after dinner in the evening. Possibly more than at the average boys' camp, the great activity of each boy during the day never failed to be a source of amazement.

DIET

In general, it may be said that the great majority of campers were satisfied with their diet. The problem of food stealing arose only occasionally, and was handled with consideration and a change in diet, if indicated. In 1948, the average diet at discharge ranged from 165 Gm. of carbohydrate daily for patients from three to 4.9 years of age to 230 Gm. in patients from 14 to 16.3 years. Corresponding figures for protein and fat were 78 to 134 Gm. and 81

to 126 Gm. respectively. The caloric contents of the diet ranged from 1701 for the younger group to 2614 for the older group.[1] Usually the campers' previous diets needed to be increased to meet the more vigorous exercise during the day. All the food is weighed by senior campers and counsellors with gram scales before each meal. Depending on the type of insulin used, between-meal feedings were given usually in the form of crackers. Routinely each child received 100 Gm. of orange juice before breakfast.

EXERCISE

The role played by exercise in the control of the diabetic camper requires special comment. Of the many variables responsible for diabetic control, exercise is one whose affect is almost as dramatic as that of insulin. Since programs of active exercise were planned to coincide with the peak action of the insulins used, larger diets and less insulin were given and, at the same time, weight was maintained and glycosuria diminished. The reverse was evident on days when weather did not permit outdoor games and activities. As one watched these children in competitive sports with non-diabetic boys from other camps (and winning in over 50% of the meets) the added psychological benefit was more than obvious. A less perceptable factor affecting diabetic control is the "adrenalizing" action of emotional disturbances as exemplified by the increased incidence of glycosuria when parents visited the camp.

INSULIN

Of the total number of diabetics at camp during the summer of 1954, only one was controlled on diet without insulin. The majority were controlled with NPH-50 insulin alone; some required Regular insulin with the above; a few were maintained on PZI and Regular in separate injections. Quoting the studies made during the first year of the camp: "With almost all campers, it was possible to achieve as good or better control with a single dose of this type of insulin (NPH-50) as with the combination of crystaline and protamine zinc insulin. In a number of instances, it was possible to use an appreciably smaller dose of NPH-50 insulin than the total dose of the other two varieties."[1] Last summer, experimental studies using the new Lente insulin were carried out on volunteer campers, the results of which have not yet been published. Careful adjustments to the insulin intake were made on the basis of laboratory findings.

LABORATORY TESTS

The high calibre of the laboratory facilities at the camp, and the close cooperation of the resident physician resulted in an exact picture of the control maintained in each diabetic child. The following routine laboratory tests were performed on each camper:

1. The 24 hour urine output was measured daily, and the percentage of sugar determined by the Exton modification of the Sumner reagent adapted for use with the photoelectric colorimeter. This was also tested for acetone using Acetest tablets.
2. Individual specimens of urine were tested qualitatively for sugar at 7:15 and 11:15 a.m. and at 4:15 and 8:00 p.m., using Benedicts Reagent.
3. Blood sugar determinations were made at the above times, two days a week, using the Capillary method of Folin adapted for use with the photoelectric colorimeter.

4. Extra blood and urine determinations were done whenever indicated.

COMPLICATIONS

Considering the number of diabetics at the camp, and their wide range of activity, complications were surprisingly few. No cases of diabetic coma or severe acidosis occurred. On the other hand, insulin reactions occurred relatively frequently. Most of these were mild and responded rapidly to 2 to 4 Gm. of sugar given as ginger ale. A few cases required intravenous glucose. A boy could be treated for a reaction, at 10 a.m. for example, and still resume normal activity without great delay. All minor skin conditions, cuts and bruises were treated promptly with no residual complications.

TEACHING PROGRAM

During the boy's period at camp, every effort was made to teach him the basic physiology of diabetes, its control and complications. This was achieved by weekly discussion groups and demonstrations with the resident physician and nurses. Senior campers were allowed to work periodically in the laboratory and showed much adeptness and understanding of the various procedures. Of equal, if not greater, importance were the personal interviews between the resident physician and the parents of each camper at which time the many problems and often the misunderstandings of the parents were resolved.

CAMPING TRIPS

One aspect of the programme which might surprise those who considered a diabetics' activities limited by his disease is that of camping trips. Each boy, at some time during his stay, embarked on an overnight hike to nearby lakes. The length of the trips were naturally limited by the type of perishable foods carried. A Clinitest kit was used by each boy for testing his own urine. Insulin was administered by the boys themselves or by a nurse in attendance. Food was cooked by each member of the trip in open fires as on any other trip. Indeed, it required a keen eye to detect any indication of diabetes amongst them.

COMMENT

The pertinent problems relating to the management of diabetic boys as seen at the Elliott P. Joslin Camp have been discussed. The opportunity afforded by such a camp alerts us to the many problems facing the diabetic child and its parents, and suggests just how important a role such a camp actually plays. The parents must be made to realize the fact that their child has a chronic disease, which will require daily insulin for the rest of his life. They must somehow impose restrictions on the child and yet avoid crippling him as a future citizen by over-protection and worry. From a psychiatric viewpoint, they must resolve in their own minds, possible guilt feelings for being the parents of a diabetic child. Last, but not least, they must understand the true nature of diabetes, and how readily their child can live with it in society.

As for the diabetic child himself, he is faced with the problem of a relatively static chronic disease superimposed upon a constantly changing outlook, both physical and mental.

The child must be made to realize that somehow he is different from the rest of his friends in as much as insulin must be taken and certain foods not eaten. All too frequently, he carries the bewildering and somewhat frightening memory of insulin reactions and diabetic coma; he must accept a degree of restraint over and above that imposed on

normal children. During the period of adoleseenee when he starts shaking off the normal bonds of parental eontrol, he must learn quiekly that he eannot do the same with the restrietions due to his disease. Above all, he must aequire, at as early an age as possible, enough knowledge of diabetes to ensure that he can be as independent as possible in the control of his disease.

In a eamp such as the one described, he is afforded the opportunity of seeing how and why his diabetes is eontrolled, of assoeiating with many ehildren with common problems, of taking part in all those aetivities normal children partiei-pate in and of realizing that, even in the absenee of his parents, adequate control of his diseases is essential. The parents, on the other hand, beeome aware that their problems are not unique and that in solving them they ean be the keystones of the child's future health and happiness.

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